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Supplement Article

IL-23 Monoclonal Antibodies for IBD: So Many, So Different?

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Abstract

Interleukin [IL]-23 is a member of the IL-12 family of cytokines and has been implicated in multiple inflammatory disorders including psoriasis, psoriatic arthritis, and the inflammatory bowel diseases [IBDs]. Blockade of both IL-12 and IL-23 using an antibody that targets a shared subunit is highly effective in treating psoriasis, and recent data suggest similar efficacy in IBD with minimal adverse events. In this review, we summarise published data on the efficacy of anti-IL-12/23 therapies in IBD as well as emerging data on more selective anti-IL-23 specific therapies. Last, we discuss novel therapeutics under development which target the IL-23 pathway in unique ways and suggest that a biomarker-driven approach will soon guide clinicians to prescribe anti-IL-23 therapies to the patients most likely to respond to them.

Key Words: Inflammatory bowel disease; IL-23; monoclonal antibody

1. Introduction

The interleukin [IL]-12 family of cytokines includes IL-12, IL-23, IL-27, and IL-35 and plays key roles in homeostasis, response to infection, and inflammatory disorders. This review will focus specifically on the relevant biology of these cytokines in inflammatory bowel disease [IBD].[1]

IL-12 and IL-23 are expressed predominantly by myeloid cells and direct type 1 and type 17 immune responses, respectively. IL-12 is a heterodimeric cytokine composed of a unique IL-12p35 subunit and a shared IL-12p40 subunit [see Figure 1].[2] IL-12 signalling is mediated by binding of the cytokine to its receptor which is composed of IL-12Rβ1 and IL-12Rβ2 and is expressed on NK, innate lymphoid cell [ILC], NKT, and naïve T cell populations. Binding of IL-12 to its receptor induces activation of the kinases JAK2 and TYK2 with resultant phosphorylation of the transcription factor STAT4, which is primarily responsible for imparting the IL-12 gene programme.[2] IL-23 is composed of the IL-12p40 subunit as well as the unique IL-23p19 subunit and signals through its receptor which is composed of IL-12Rβ1 and IL-23R [together referred to as the IL-23 receptor]. JAK2 and TYK2 are also activated downstream of IL-23 receptor signalling, but in contrast to signalling through the IL-12 receptor, the transcription factor STAT3 is activated, which contributes to the differential outcome from signalling downstream of these cytokines.[3,4] Notably, the IL-23 receptor is minimally expressed on naïve T cells, and thus likely imparts its effects on effector T cells located at mucosal sites in addition to its effects on innate and innate-like lymphocytes.[5]

Interest in targeting IL-12 in inflammatory disorders arose from preclinical studies that suggested a role for IL-12 in mouse models of numerous inflammatory conditions, including inflammatory arthritis, multiple sclerosis, and colitis.[6] Indeed, genetic or antibody-mediated inhibition of IL-12p40 or IL-12Rβ1 ameliorated disease in these models. However, the recognition that IL-12p40 was also a component of IL-23 and the subsequent demonstration that IL-23, and not IL-12, drove these experimental inflammatory conditions was a turning point in our understanding of these inflammatory disorders and sparked great interest in selective targeting of the IL-23 pathway.[7,8] Here, we review the community's experience of managing Crohn's disease [CD] and ulcerative colitis [UC] with an anti-IL-12p40 therapy [which we term 'first generation' anti-IL-23 therapies to reflect the realisation that the clinical utility of this agent is thought to result from IL-23 inhibition and not IL-12 blockade] as well as emerging data on 'second generation' selective anti-IL-23 therapies which target IL-23p19 and have shown promising results in other immune-mediated inflammatory disorders and in ongoing trials involving patients with IBD. Last, we comment on 'third generation' IL-23 therapies which may be part of our armamentarium in the future. Table 1 summarises the clinical trials for all current and emerging IL-23 therapies in IBD.

2. First Generation Anti-IL-23 Therapy in Crohn's Disease

The anti-IL-12p40 monoclonal antibody ustekinumab was approved for treatment of moderate to severe plaque psoriasis in 2009 and subsequently for moderate to severe CD in 2016. The UNITI-1 (tumour necrosis factor inhibitor [TNFi]-experienced patients) and UNITI-2 [TNFi-naïve] induction trials randomised nearly 1400 patients in a 1:1:1 fashion to receive a single loading dose of 130 mg of ustekinumab, 6 mg/kg of ustekinumab, or placebo, and the 397 responders were followed for up to 96 weeks as part of the IM-UNITI

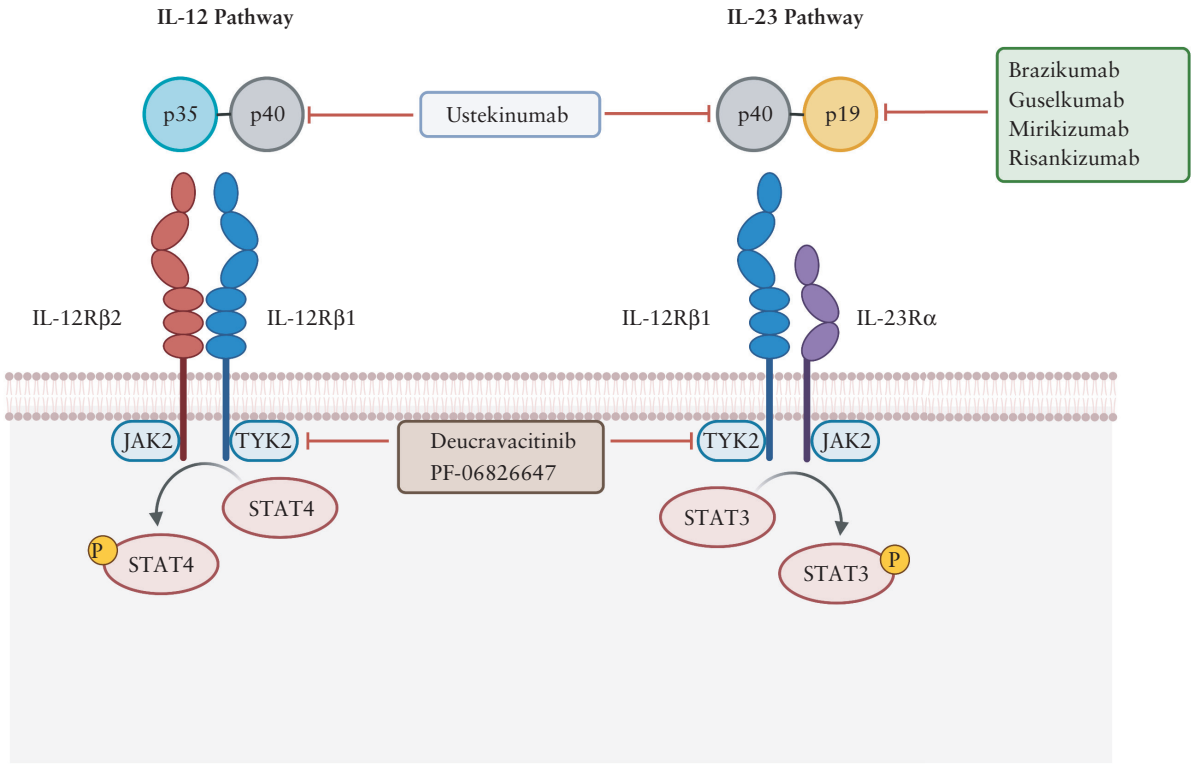

Figure 1. Molecular targets of anti-IL-23 therapies. First generation [blue box], second generation [green box], and third generation [brown box] anti-IL-23 therapies are displayed. Created with biorender.com.

maintenance trial.[9,10] The primary endpoint for UNITI-1 and UNITI-2 was clinical response at Week 6, defined as a decrease in the Crohn's Disease Activity Index [CDAI] of >100 points or an absolute score <150 and the primary endpoint for IM-UNITI was remission at Week 44 defined as CDAI <150. Regardless of whether the patient was previously treated with TNFi therapy, patients who received a loading dose of either 130 mg or 6 mg/kg of ustekinumab were more likely to achieve response than those who received placebo [34.3% vs 33.7% vs 21.5% in UNITI-1; p <0.003 for both comparisons with placebo, and 51.7% vs 55.5% vs 28.7% in UNITI-2; p <0.001 for both comparisons with placebo]. Those patients who responded to ustekinumab continued on either every 8 weeks or every 12 weeks dosing and were more likely than those receiving placebo to maintain remission (53.1% vs 48.8% vs 35.9%; p = 0.005 [every 8 weeks] and p = 0.04 [every 12 weeks]). A subset of 334 patients from these trials underwent colonoscopic evaluation at baseline, at Week 8, and at Week 52 to evaluate whether ustekinumab was associated with mucosal healing as measured by the Simplified Endoscopic Activity Score for Crohn's Disease [SES-CD]. Patients who received ustekinumab induction therapy had a greater decrease in SES-CD at Week 8 than those who received placebo [2.8 vs 0.7 points; p = 0.012].[11] Although not statistically significant, this trend continued on to 1 year of ustekinumab therapy. Importantly, adverse events were not more likely to occur in those who received ustekinumab compared with placebo.[9,10]

Perianal CD occurs in almost 50% of patients with CD and can be challenging to successfully treat. Post-hoc analysis of the ustekinumab trials Crohn's Evaluation of Response to Ustekinumab Anti-Interleukin-12/23 [CERTIFI], UNITI-1, and UNITI-2 demonstrated a trend towards higher rates of fistula response, defined as 50% reduction in actively draining fistulas [80% vs 45.5%; p = 0.64] and fistula resolution defined as 100% reduction in actively draining fistulas [24.7% vs 14.1%; p = 0.073] although small sample sizes limited firm conclusions.[12] Additional studies are needed to further evaluate the role of ustekinumab in treating perianal CD.

Dose escalation can be beneficial in patients who incompletely respond to biologic therapy. Retrospective review of more than 500 CD patients at a single centre, who were treated with ustekinumab, found that 110 patients who had an incomplete response had the dosing interval shortened to every 4 weeks. Dose interval shortening was effective—patients receiving every 4-weeks dosing had lower Harvey-Bradshaw Index scores [4.5 vs 3; p = 0.002], lower C-reactive protein [CRP] levels [8 mg/L vs 3 mg/L; p = 0.031], and trended toward lower faecal calprotectin levels [378 µg/g vs 157 µg/g; p = 0.57] and SES-CD scores [8.5 vs 4.5; p = 0.061].[13]

It is understood that patient symptoms are an imperfect surrogate for disease activity and that optimal management of inflammatory conditions, including CD, should integrate endoscopic disease activity assessment and measurement of biochemical markers of inflammation along with patient symptoms to guide therapy decisions—a strategy known as 'treat to target [T2T]'.[14–16] The Study of Treat to Target Versus Routine Care Maintenance Strategies in Crohn's Disease Patients Treated with Ustekinumab [STARDUST] trial is a randomised controlled trial comparing a T2T management strategy, where ustekinumab can be adjusted following a Week 16 colonoscopy, with a standard of care approach that relies on patient symptoms and the physician's clinical judgement. All participants had moderate to severe CD and received ustekinumab intravenous [IV] induction dosing of 6 mg/kg followed by 90 mg of subcutaneous [SC] ustekinumab at

Table 1. Results of anti-IL-23 clinical trials.

Study	TNFi	Disease	Route of administration	Dosing	Frequency of dosing	Primary endpoints	Time points	Primary endpoint results	
First generation anti-IL-23 therapy in IBD [ustekinumab]									
UNITI-1	Exposed	CD	IV induction, SC maintenance	6 mg/kg ustekinumab or placebo	q12wk or q8wk	Clinical response at Wk 6 [decrease in CDAI >100 points or an absolute score <150]	Wk 6	**Clinical response** 34.3% [130 mg] 33.7% [6 mg/kg] 21.5% [placebo]	*p* ≤0.003 ≤0.003 —
UNITI-2	Naïve	CD	IV induction, SC maintenance	6 mg/kg ustekinumab or placebo	q12wk or q8wk	Clinical response at Wk 6 [decrease in CDAI >100 points or an absolute score <150]	Wk 6	51.7% [130 mg] 55.5% [6 mg/kg] 28.7% [placebo]	0.005 0.04 —
IM-UNITI Maintenance	Mixed	CD	SC maintenance	90 mg ustekinumab	q12wk or q8wk	Clinical remission defined as CDAI <150 points, clinical response defined as a reduction from Wk 0 of UNITI-1 or UNITI-2 in the CDAI score of ≥ 100 points	Wk 152	Clinical response 67.9% [q12wk] 76.8% [q8wk]	Clinical remission 61.9% [q12wk] 69.5% [q8wk]
CERTIFI	Exposed	CD	IV induction, SC maintenance	1 mg/kg, 3 mg/kg, 6 mg/kg ustekinumab, placebo	q8wk	Clinical response defined as ≥100-point decrease from the baseline CDAI score	Wk 6	Clinical response 36.6% [1 mg/kg] 34.1% [3 mg/kg] 39.7% [6 mg/kg] 23.5% [placebo]	*p* 0.02 0.06 0.005 —
STARDUST	Mixed	CD	IV induction, SC maintenance	Induction 6 mg/kg, 90 mg SC ustekinumab at Wk 8	Treat to target strategy after clinical response to induction	Endoscopic response defined as SES-CD score ≥50% decrease from baseline	Wk 48	Endoscopic response 38% [treat to target] 30% [SOC]	*p* 0.087 —
SEAVUE	Naïve	CD	IV induction, SC maintenance	Ustekinumab [induction dosing with 6 mg/kg IV and maintenance dosing of 90 mg SC every 8 wks], adalimumab [induction dosing with 160 mg SC, 80 mg at Wk 2 and maintenance dosing with 40 mg every 2 wks]	Ustekinumab maintenance q8wk, adalimumab maintenance q2wk	Clinical remission defined as CDAI <150	Wk 52	Clinical remission 65% [ustekinumab] 61% [adalimumab]	*p* 0.417 —

Table 1. Continued

Study	TNFi	Disease	Route of administration	Dosing	Frequency of dosing	Primary endpoints	Time points	Primary endpoint results	
UNIFI	Stratified	UC	IV induction, SC maintenance	130 mg, 6 mg/kg ustekinumab, or placebo	q12wk or q8wk	Clinical remission defined as a total Mayo score of less than or equal to 2 with no subscore greater than 1	Wk 8, Wk 44	Clinical remission 15.6% [130 mg, Wk8] 15.5% [6 mg/kg, Wk8] 5.3% [placebo, Wk8] 38.4% [90 mg, q12wk, Wk44] 43.8% [90 mg, q8wk, Wk44] 24.0% [placebo, Wk44]	*p* <0.001 <0.001 — 0.002 <0.001 —
Second generation anti-IL-23 therapy in IBD									
Efficacy and Safety of MEDI2070 [Sands BE, *et al.*]	Exposed	CD	IV Wk 0 and Wk 4, SC every 4 wks starting at Wk 12	700 mg brazikumab, placebo	q4wk, 700 mg IV at Wk 0 and 4; 210 mg SC every 4 wks starting at Wk 8	Clinical response defined as either a 100-point decrease in CDAI score from baseline or clinical remission, defined as CDAI score <150	Wk 8, Wk 24	Clinical response 49.2% [brazikumab, Wk 8] 26.7% [placebo, Wk 8] 53.8% [brazikumab, Wk 24] 57.7% [placebo, Wk 24]	*p* 0.10 — — —
GALAXI	Mixed	CD	IV induction, SC at Wk 8	200 mg, 600 mg, or 1200 mg guselkumab; induction 6 mg/kg, 90 mg SC ustekinumab at Wk 8; placebo	Guselkumab: q4wk ustekinumab: q8wk	Change from baseline CDAI	Wk 12	Reduction from baseline in CDAI score -160.4 [200 mg] -138.9 [600 mg] -144.9 [1200 mg] -36.2 [placebo]	*p* <0.05 <0.05 <0.05 —
Efficacy and safety of mirikizumab [Sands BE, *et al.*]	Mixed	CD	IV	200 mg, 600 mg, 1000 mg mirikizumab, or placebo	q4wk	Endoscopic response defined as a decrease of SES-CD of at least 1 point	Wk 12	Endoscopic response 25.8% [200 mg] 37.5% [600 mg] 43.8% [1000 mg] 10.9% [placebo]	*p* 0.079 0.003 <0.001 —
Efficacy and safety of mirikizumab [Sandborn WJ, *et al.*]	Mixed	UC	IV	50 mg, 200 mg, 600 mg mirikizumab, or placebo	q4wk	Clinical remission defined as Mayo subscores of 0 for rectal bleeding, with 1-point decrease from baseline for stool frequency, and 0 or 1 for endoscopy	Wk 12	Clinical remission 15.9% [50 mg] 22.6% [200 mg] 11.5% [600 mg] 4.8% [placebo]	*p* 0.066 0.004 0.142 —

Table 1. Continued

Study	TNFi	Disease	Route of administration	Dosing	Frequency of dosing	Primary endpoints	Time points	Primary endpoint results	
LUCENT-1	Stratified	UC	IV	300 mg mirikizumab or placebo	q4wk or q8wk	Clinical remission defined as stool frequency subscore = 0 or 1 with a ≥ 1-point decrease from baseline, and rectal bleeding subscore = 0, and endoscopic subscore = 0 or 1 [excluding friability]	Wk 12	Clinical remission 24.4% [300 mg] 13.3% [placebo]	*p* 0.00006 —
ADVANCE	Mixed [conventional and biologic therapies]	CD	IV	600 mg, 1200 mg risankizumab or placebo	q4wk	Clinical remission defined as a CDAI score of < 150	Wk 12	Clinical remission 45.2% [600 mg] 41.6% [1200 mg] 25.2% [placebo]	*p* ≤0.001 ≤0.001 —
MOTIVATE	Mixed [biologic therapies only]	CD	IV	600 mg, 1200 mg risankizumab or placebo	q4wk	Clinical remission defined as a CDAI score of < 150	Wk 12	42.5% [600 mg] 40.3% [1200 mg] 19.8% [placebo]	≤0.001 ≤0.001 —
FORTIFY	Stratified	CD	SC	360 mg, 600 mg, risankizumab or withdrawn from IV risankizumab to receive SC placebo	q4wk	Endoscopic response defined as a decrease in SES-CD >50% from baseline; endoscopic remission defined as SES-CD ≥4 and at least a 2-point reduction versus baseline and no subscore greater than 1 in any individual variable; ulcer-free endoscopy defined as SES-CD ulcerated surface subscore of 0 in subjects with SES-CD ulcerated surface subscore ≥1 at baseline; deep remission defined as CDAI <150 and endoscopic remission	Wk 12	Endoscopic response 46.5 % [overall 600 mg] 22.0% [overall placebo] 43.7% [600 mg, bio-failure] 20.3% [placebo, bio-failure] 53.8% [360 mg, no bio-failure] 26.8% [placebo, no bio-failure]	*p* <0.001 — NS

Table 1. Continued

Study	TNFi	Disease	Route of administration	Dosing	Frequency of dosing	Primary endpoints	Time points	Primary endpoint results	
								Ulcer-free ndoscopy	*p*
								30.5% [overall 600 mg]	<0.001
								10.5% [overall placebo]	—
								26.5% [600 mg, bio-failure]	NS
								6.6% [placebo, bio-failure]	—
								41.0% [360 mg, no bio-failure]	
								22.0% [placebo, no bio-failure]	
								Endoscopic re-mission	*p*
								39.1% [overall 600 mg]	<0.001
								12.8% [overall placebo]	—
								35.4% [600 mg, bio-failure]	NS
								9.8% [placebo, bio-failure]	—
								48.7% [360 mg, no bio-failure]	
								22.0% [placebo, no bio-failure]	
								Deep remission	*p*
								29.1% [overall 600 mg]	<0.001
								10.4% [overall placebo]	—
								23.6% [600 mg, bio-failure]	NS
								8.1% [placebo, bio-failure]	—
								43.6% [360 mg, no bio-failure]	
								17.1% [placebo, no bio-failure]	

Table 1. Continued

Study	TNFi	Disease	Route of administration	Dosing	Frequency of dosing	Primary endpoints	Time points	Primary endpoint results	
Induction Therapy with Risankizumab [Feagan BG, et al.]	Stratified	CD	IV	200 mg, 600 mg risankizumab, or placebo	q4wk	Clinical remission defined as CDAI <150	Wk 12	Clinical remission	*p*
								31% [pooled]	0.0489
								24% [200mg]	0.31
								37% [600mg]	0.0252
								15% [placebo]	—

CD, Crohn's disease; UC, ulcerative colitis; CDAI, Crohn's Disease Activity Index; SES-CD, simple endoscopic score-Crohn's disease; SOC, standard of care; IV, intravenous; SC, subcutaneous; wk, week; q2wk, every 2 weeks; q4wk, every 4 weeks; q8wk every 8 weeks; q12wk, every 12 weeks; NS, not significant; IBD, inflammatory bowel disease; TNFi, tumour necrosis factor inhibitor.

Week 8. Those who responded to induction dosing [had a CDAI decrease of at least 70 points] were then randomised to a T2T management style where dose adjustments were guided by patient symptoms and biochemical markers of inflammation versus a standard of care style. Patients will be followed for up to 104 weeks, but results were recently reported through Week 48 and suggest that more patients in the T2T group met the secondary endpoint of corticosteroid-free endoscopic response [33.6% vs 28.5%] although the difference was not statistically significant [and *p*-value was not reported].[17] More definitive answers will come when results of the complete study are released. A STARDUST substudy evaluated the exposure-response relationship in CD patients participating in the trial. Patients in the higher quartiles for serum ustekinumab concentration were more likely to achieve biomarker [CRP and faecal calprotectin] and endoscopic improvements than those patients with lower levels of circulating ustekinumab. Importantly, baseline CRP concentrations were inversely correlated with ustekinumab concentrations at Weeks 8 and 16, suggesting that patients with a high inflammatory burden may clear ustekinumab more quickly.[17]

There are few studies that directly compare efficacy and safety of different CD therapies, but several studies are either under way or have recently been published. The Safety and Efficacy of Adalimumab Versus Ustekinumab for One Year [SEAVUE] study is the first head-to-head trial comparing biologic therapies in patients with CD. It was a multicentre, randomised, double-blinded study that recruited patients with active CD [CDAI between 220 and 450] who were naïve to biologic therapy or intolerant of conventional therapy and who had an ulcer on baseline colonoscopy.[18] Patients were randomised 1:1 to ustekinumab [induction dosing with 6 mg/kg IV followed by maintenance dosing of 90 mg SC every 8 weeks] or adalimumab [induction dosing with 160 mg SC at Week 0, 80 mg at Week 2, and maintenance dosing with 40 mg every 2 weeks]. The primary endpoint was clinical remission at Week 52, which was defined as a CDAI <150. Almost 400 patients participated in the trial and there was no significant difference between groups for achieving the primary endpoint—65% of participants who received ustekinumab and 61% of patients who received adalimumab were in clinical remission at Week 52. Patients who received ustekinumab and had a clinical response at Week 16 were more likely than those who received adalimumab to be in clinical remission at Week 52 [88.6% vs 78.0%; $p = 0.016$]. There was no difference between adalimumab and ustekinumab for any other major secondary endpoint. Importantly, there were few adverse events in either group.

Ustekinumab was compared with vedolizumab in a prospective observational study in patients with CD who did not respond, lost response, or were intolerant to TNFi therapy.[19] In all, 213 patients met criteria for inclusion in the study and were assessed for corticosteroid-free remission [defined as Harvey-Bradshaw Index less than or equal to 4], biochemical remission [CRP less than or equal to 5 mg/L and faecal calprotectin less than or equal to 250 μg/g], combined corticosteroid-free and biochemical remission, and safety outcomes. Patients who received ustekinumab were significantly more likely to achieve corticosteroid-free remission (odds ratio [OR]: 2.58, 95% confidence interval [CI]: 1.36-4.90; $p = 0.004$], biochemical remission [OR: 2.34, 95% CI: 1.104.96; $p = 0.02$], and combined corticosteroid-free

and biochemical remission [OR: 2.74, 95% CI: 1.23-6.09; $p = 0.01$] but were not more likely to experience a safety event [OR: 1.26, 95% CI: 0.63-2.54; $p = 0.51$].

Last, ustekinumab and vedolizumab were compared in a retrospective multicentre study of CD patients refractory to TNFi therapy.[20] A total of 312 patients [224 treated with ustekinumab and 88 with vedolizumab] were included in the study and the primary endpoint was corticosteroid-free clinical remission [CDREM; CDAI <150] at Week 54. Key secondary endpoints included deep remission [CFREM and faecal calprotectin <100 µg/g] at Week 14 and time to drug discontinuation. After propensity score matching, patients who received ustekinumab more frequently achieved CFREM than those who received vedolizumab [49.3% vs 41.2%; $p = 0.04$] at Week 54. Further, the rate of deep remission at Week 14 was higher in those receiving ustekinumab [25.9% vs 3.8%; $p = 0.02$]. As above, adverse events were similar across both groups.

A recent systematic review and meta-analysis combined five studies including a total of 1026 patients who received either ustekinumab [659 patients] or vedolizumab [367 patients].[21] At Week 14, there were no significant differences in the rates of clinical remission, steroid-free clinical remission, or biological remission. However, at Week 52 patients receiving ustekinumab were more likely to be in clinical remission [OR 1.87; 95% CI: 1.18-2.98], steroid-free clinical remission [OR 1.56; 95% CI: 1.23-1.97], and biological remission [OR 1.86; 95% CI: 1.03-3.37] than patients receiving vedolizumab.

3. First Generation Anti-IL-23 Therapy in Ulcerative Colitis

Ustekinumab received Food and Drugs Administration [FDA] approval for moderate to severe UC in 2019, based in part on the UNIFI trial which was a multicentre, randomised induction and maintenance study of patients with moderate to severe UC.[22] For induction dosing, a total of 961 patients received IV ustekinumab as a dose of either 130 mg, 6 mg/kg, or placebo. Those patients who responded received either 90 mg of ustekinumab every 12 weeks or every 8 weeks, or placebo. The primary endpoint of both the induction and maintenance trials was clinical remission [defined as a total Mayo score of less than or equal to 2 with no subscore greater than 1] at 8 or 44 weeks, respectively. More patients who received ustekinumab [15.6% of the 130 mg group, 15.5% of the 6 mg/kg group] achieved clinical remission at Week 8 compared with placebo [5.3%; p <0.001 for both comparisons]. A response to ustekinumab induction dosing was seen as early as 7 days after the infusion, with patients who responded reporting fewer daily stools and less rectal bleeding.[23] At 44 weeks, 38.4% of patients receiving ustekinumab every 12 weeks and 43.8% of patients receiving ustekinumab every 8 weeks were in clinical remission compared with 24% of those receiving placebo [$p = 0.02$ and p <0.001, respectively]. The UNIFI long-term extension trial demonstrated that remission was maintained through at least 92 weeks of therapy and no significant differences were seen between every 8 weeks and every 12 weeks dosing.[24,25] Of note, symptomatic remission was more common in patients who were previously naïve to biologic therapies compared with those who had failed prior biologics. Outside of the UNIFI trial, several groups have reported similar rates of clinical remission even in patients who have failed other biologic therapies.[26–28] There were two deaths and seven cancers detected in the group that received ustekinumab and one cancer in the placebo group. This result has not been seen in pivotal clinical trials in IBD, including UNITI, or in studies with long follow-up of psoriasis.[24,25,29,30]

Endoscopic mucosal healing is associated with favourable outcomes in UC, and numerous observational studies suggest that histological improvement or normalisation predicts lower risks of disease relapse and dysplasia.[31–34] The UNIFI trial was the first study to include a novel endpoint termed histo-endoscopic mucosal healing, defined as endoscopic improvement [Mayo endoscopic subscore of 0 or 1] and histological improvement [<5% neutrophils in the epithelium, no crypt destruction, and no erosions, ulcerations, or granulations].[22,35] Notably, significantly more patients who received ustekinumab every 12 weeks [38.8%] or every 8 weeks [45.9%] achieved histo-endoscopic mucosal healing than those who received placebo [24.1%; $p = 0.002$ and p <0.001, respectively] through 52 weeks of the study.[36] Additional studies are ongoing to better understand whether there is an additional benefit to histo-endoscopic healing compared with endoscopic mucosal healing in UC.

4. Combination Therapy and Immunogenicity

The addition of an immunomodulator [azathioprine, 6-mercaptopurine, or methotrexate] to anti-TNF therapy decreases the risk of developing anti-drug antibodies and the subsequent loss of response to that therapy. Several lines of evidence suggest that this is not true for combination therapy with ustekinumab. First, the frequency of anti-drug antibodies in patients treated with ustekinumab in the IM-UNITI trial was 4.6% through 156 weeks of therapy, and the frequency of patients who developed anti-drug antibodies was similar with or without concomitant immunomodulator use when compared at Week 44 [4.5% without concomitant immunomodulator use vs 5.0% with immunomodulator use; p-value not reported].[37] Importantly, the development of antibodies was not associated with a loss of response [thus, the antibodies were likely not drug-neutralising]; and second, the addition of an immunomodulator to ustekinumab was not found to improve patient outcomes. A prospective, multicentre observational study evaluated patients with either UC or CD who received ustekinumab or vedolizumab with or without an immunomodulator, and found no difference in clinical response or remission at 1 year [62.1% vs 67.0%; $p = 0.52$] or therapy persistence at 1 year between the groups [log-rank $p = 0.36$].[38] Anaphylaxis or other infusion reactions can occur following administration of biologic therapies, in part due to their immunogenicity. There are reports of anaphylaxis following the IV ustekinumab loading dose in patients who had never received ustekinumab before suggesting, based on immunological principles, that an excipient in the IV formulation of ustekinumab is the immunogenic substance.[39] Indeed, since our initial case report, other colleagues have demonstrated similarly that patients who had immediate hypersensitivity reactions to IV ustekinumab can tolerate subsequent SC formulations.[39]

Due to the severity of bowel inflammation or the presence of coexisting rheumatological or dermatological disorders, some patients may benefit from the use of two biologic or small molecule inhibitor therapies, although data on efficacy are limited and there are concerns about safety. A

recent systematic review examined data from 13 studies that combined either two biologic medications [ustekinumab, vedolizumab, natalizumab, or TNFi] or one biologic medication and one small molecule inhibitor [tofacitinib], and suggested that this approach could be efficacious and did not detect an adverse event signal.[40] Additionally, we have demonstrated the utility of bridge therapy with cyclosporine induction and subsequent ustekinumab maintenance for patients with acute severe UC.[41]

5. Ustekinumab in Pregnancy

Broadly, biologic and thiopurine use before and during pregnancy has been studied extensively and found to be safe for both the mother and the fetus, although a limitation in the largest and most recent evaluation of these data was that very few patients were exposed to ustekinumab near the time of their pregnancy.[42] A recent study evaluated pregnancies with ustekinumab use during pregnancy or in the 3-month period prior to conception, and found no difference in live births, spontaneous abortions, or major congenital abnormalities compared with the general population.[43] Thus, combined with the known risks of active IBD during pregnancy, it is reasonable to use ustekinumab before and during pregnancy. Data on breastfeeding while using ustekinumab are sparse; ustekinumab is found in breast milk although absorption by the neonate is likely negligible.[44] Additional studies on ustekinumab levels in the neonate's blood and outcomes data are needed.

6. Second Generation Anti-IL-23 Therapy in IBD

Given the preclinical data described above which implicated IL-23 more than IL-12 as a driver of inflammatory conditions, there has been considerable interest in developing IL-23 selective therapies that may offer all of the benefit of anti-IL-12p40 therapies with less off-target effect from inhibition of IL-12 signalling. Thus, we term these anti-IL-23p19 antibodies 'second generation' selective anti-IL-23 therapies. Several second generation anti-IL-23 therapies have been studied in psoriasis and psoriatic arthritis, with promising results.[45]

Four different second generation anti-IL-23 therapies have been evaluated in inflammatory bowel disease—brazikumab, guselkumab, mirikizumab, and risankizumab. A phase 2 study of 112 patients with moderate to severe CD, who had failed TNFi therapy, compared brazikumab with placebo.[46] Patients received either 700 mg of IV brazikumab or placebo at Weeks 0 and 4, and all patients received 210 mg brazikumab SC every 4 weeks beginning at Week 12. The primary outcome of clinical response [defined as either clinical remission or a 100-point decrease in the CDAI] at Week 8 occurred in 49.2% of patients receiving brazikumab but in 26.7% of patients receiving placebo [p = 0.01]. The heterogeneity of IBD phenotypes between patients is well described, yet our understanding of the cellular and molecular determinants of these differences remains limited. Identifying biomarkers that predict response to a particular therapy would allow clinicians to offer IBD patients a form of personalised medicine tailored to their particular disease phenotype. Interestingly, patients who had higher baseline serum IL-22 levels [a cytokine induced by IL-23 signalling] were more likely to respond to brazikumab, suggesting that identifying patients with high levels of circulating IL-22 may allow for more rational therapeutic decisions.[46] There are ongoing investigations into serum IL-22 concentration as a therapeutic biomarker of IL-23 blockade responsiveness.

A second phase 2 trial evaluated guselkumab in 250 patients with moderate to severe CD refractory to conventional therapy and/or biologics [anti-TNF or vedolizumab].[47,48] Patients received either 200 mg, 600 mg, or 1200 mg of IV guselkumab or placebo at Weeks 0, 4, and 8, and endoscopic improvement [measured with the SES-CD score], serum CRP, and faecal calprotectin were measured at Week 12. Patients who received guselkumab showed greater endoscopic improvement than patients who received placebo, regardless of whether they had previously failed biologic or conventional therapies [least squares mean reduction in SES-CD score for all guselkumab doses at Week 12 was 4.6 vs 0.5 for placebo; p <0.001] and had greater reductions in CRP and calprotectin. Of note, the response to guselkumab was not dose-dependent above 200 mg.

The humanised monoclonal antibody risankizumab was assessed in a phase 2 study of patients with moderate to severe CD.[49] Patients were randomised to receive either 200 mg or 600 mg of IV risankizumab or placebo at eeks 0, 4, and 8, and the primary endpoint of clinical remission [defined as CDAI <150] was assessed at Week 12. Patients who received risankizumab were more likely to achieve clinical remission than those who received placebo, and the higher dose of risankizumab appeared to be more effective [15.4% placebo, 24.4% 200 mg dose; p = 0.31, and 36.6% 600 mg dose; p = 0.03, 31% for all dosages combined; p = 0.049]. Results from two phase 3 trials that compared risankizumab with placebo in patients with moderate to severe CD, who had an inadequate response to conventional and/or other biologic therapies [ADVANCE] or who had an inadequate response to previous biologic therapies [MOTIVATE], were recently released. Patients who received either 600 mg or 1200 mg of risankizumab at Weeks 0, 4, and 8 were more likely to be in clinical remission at Week 12 as defined by the CDAI than those who received placebo [ADVANCE: 41.6% vs 45.2% vs 25.2%; p <0.001 for both comparisons; MOTIVATE: 40.3% vs 42.5% vs 19.8%; p <0.001 for both comparisons].[50] The FORTIFY maintenance study had patients continue with either 360 mg of risankizumab SC or placebo, and subgroup analysis demonstrated that patients who received risankizumab were more likely to be in endoscopic remission at Week 52 than those who were maintained on placebo [39.1% vs 12.8%; p <0.001].[51]

Mirikizumab was evaluated in a phase 2 study of patients with moderate to severe CD. Patients were randomised to receive 200 mg, 600 mg, or 1000 mg of IV mirikizumab or placebo at Weeks 0, 4, and 8, and endoscopic response [decrease of SES-CD of at least 1 point] was assessed at Week 12. Patients who received mirikizumab were more likely to respond than those who received placebo, and there was evidence of a dose response [10.9% placebo; 25.8% 200 mg dose; p = 0.079, 37.5% 600 mg dose; p = 0.003, and 43.8% 1000 mg dose; p <0.001].[52] Patients who responded to induction dosing were randomised to receive either continued IV dosing every 4 weeks or to receive 300 mg SC mirikizumab every 4 weeks.[53] Nearly 70% of both the IV and the SC maintenance groups maintained remission to 52 weeks. A similar study of mirikizumab was performed on patients with

moderate to severe UC using IV doses of 50 mg, 200 mg, and 600 mg.[54] The trial did not meet the primary endpoint of clinical remission at Week 12 [see Table 1], but there was an increase in the clinical response seen at Week 12 [20.6% in the placebo group, 41.3% in the 50 mg group; $p = 0.014$, 59.7% in the 200 mg group; $p < 0.001$, and 49.2% in 600 mg group; $p = 0.001$], and up to 50% of patients maintained remission to 52 weeks. Further, patients who received either 200 mg or 600 mg doses of mirikizumab were more likely to achieve histological remission at Week 12, and mirikizumab maintained histological remission through 52 weeks.[55] Adverse events were similar between placebo and mirikizumab-treated groups. Mirikizumab was also evaluated in a phase 3 trial of patients with moderate to severe UC. Patients were randomised to receive either 300 mg of IV mirikizumab ever 4 weeks for 12 weeks or placebo. Patients who received mirikizumab were more likely to achieve the primary endpoint of clinical remission at Week 12 [24.2% vs 13.3%; $p = 0.00006$].[56]

It is obviously of interest to know whether more specific inhibition of IL-23 with such therapies may provide superior efficacy compared with the IL-12/IL-23 effects of ustekinumab. In a trial of moderate to severe plaque psoriasis patients, risankizumab was compared directly with ustekinumab and significantly more patients who received risankizumab met the primary endpoint [PASI90: 90% or greater reduction in the baseline Psoriasis Area and Severity Index].[57] Intriguingly, more patients who received risankizumab achieved 'excellent improvement' in a global histological assessment compared with those who received ustekinumab. Transcriptional analysis of skin biopsies showed decreased expression of psoriasis- and IL-23-associated genes selectively in the risankizumab-treated group. A more recent study compared risankizumab with adalimumab in patients with moderate to severe plaque psoriasis and found risankizumab to be superior.[58] On the other hand, in the guselkumab trial of patients with moderate to severe CD described above, guselkumab was compared directly with ustekinumab and was not more efficacious, although it is notable that this phase 2 study was underpowered to specifically address this question.[47,48] Altogether, there is reason to be optimistic about the potential for these selective IL-23 therapies, but additional studies are warranted.

7. Third Generation Anti-IL-23 Therapy

Synthetic small molecules that target IL-23 may have advantages over biologic therapies. First, many patients prefer the convenience of an oral delivery system over those that require injection or infusion. Second, oral therapies are not immunogenic so treatment could be started and stopped without worry of secondary nonresponse [loss of response]. Third, in severely inflamed patients, loss of drug into the intestinal lumen due to protein leakage does not occur with the absorption and pharmacokinetic [PK] profile of small molecules, so the dose/exposure challenges seen with the monoclonal antibodies can be avoided. There are several such small molecule therapies currently in development which target the IL-23 pathway. Oral IL-23R antagonists are in phase 2 trials for CD and, based on the mechanism of action, are predicted to have similar effects as anti-IL-23 biologics.[59] There are several small molecule inhibitors of signalling molecules activated downstream of the IL-23R which are currently being studied. The TYK2 inhibitors deucravacitinib and PF-06826647 already show promising results in patients with psoriasis.[60,61] Because TYK2 is activated downstream of both IL-12 and IL-23, these inhibitors may behave similarly to ustekinumab. Interestingly, TYK2 is involved in signalling from the type I interferon receptor. Several trials have evaluated type I interferons as a therapy for IBD, but with mixed results.[62–66] Last, JAK2 is also activated downstream of IL-12 and IL-23 signalling, but there are no JAK2-specific inhibitors currently being studied in IBD, likely because of safety concerns related to the role of JAK2 in haematopoiesis.[67]

8. Conclusion

Our understanding of the role of IL-23 signalling in inflammation was born out of seminal animal model work and has now been translated with great success to treat a diverse set of inflammatory disorders. Indeed, the first generation anti-IL-23 therapy ustekinumab is effective, safe, and has minimal immunogenicity, as seen in both CD and UC trials, with the latter also including a novel mucosal healing endpoint of interest. More recent head-to-head comparison of adalimumab with ustekinumab does not show superiority of ustekinumab, but does suggest better tolerability and immunogenicity of this agent and, in multiple assessments of ustekinumab compared with vedolizumab after TNFi in CD, ustekinumab appears to be the preferred second-line therapy. Second and third generation inhibitors, selective either just for the IL-23 pathway or for the IL-23 pathway as well as other proteins implicated in IBD pathogenesis, are currently in development and show promising efficacy and safety in early trials of CD and UC patients with minimal safety risks. Notably, second generation anti-IL-23 therapies appear to be more efficacious than first generation therapies in psoriasis, and it will be important to determine if this is true in IBD patients as well. Preliminary studies suggest that second generation IL-23 therapies are effective in both UC and CD, but the underlying inflammatory mechanisms for UC and CD are different and certain subpopulations of UC or CD patients may be more likely to respond to these therapies than others.[68]

In the coming years it is likely that treatment decisions for the individual patient will rely on the use of predictive biomarkers, instead of our empirical decisions of today. It is particularly notable that serum IL-22 levels predicted response to second generation anti-IL-23 therapies. Future studies in this area are certain to help us get the right therapy to the patient.

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Conflict of Interest

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Author Contributions

Conceptualisation and outline, DTR; drafting manuscript, critical editing, approval of final manuscript, all authors.

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